Exploring new molecular imaging concepts of prostate cancer

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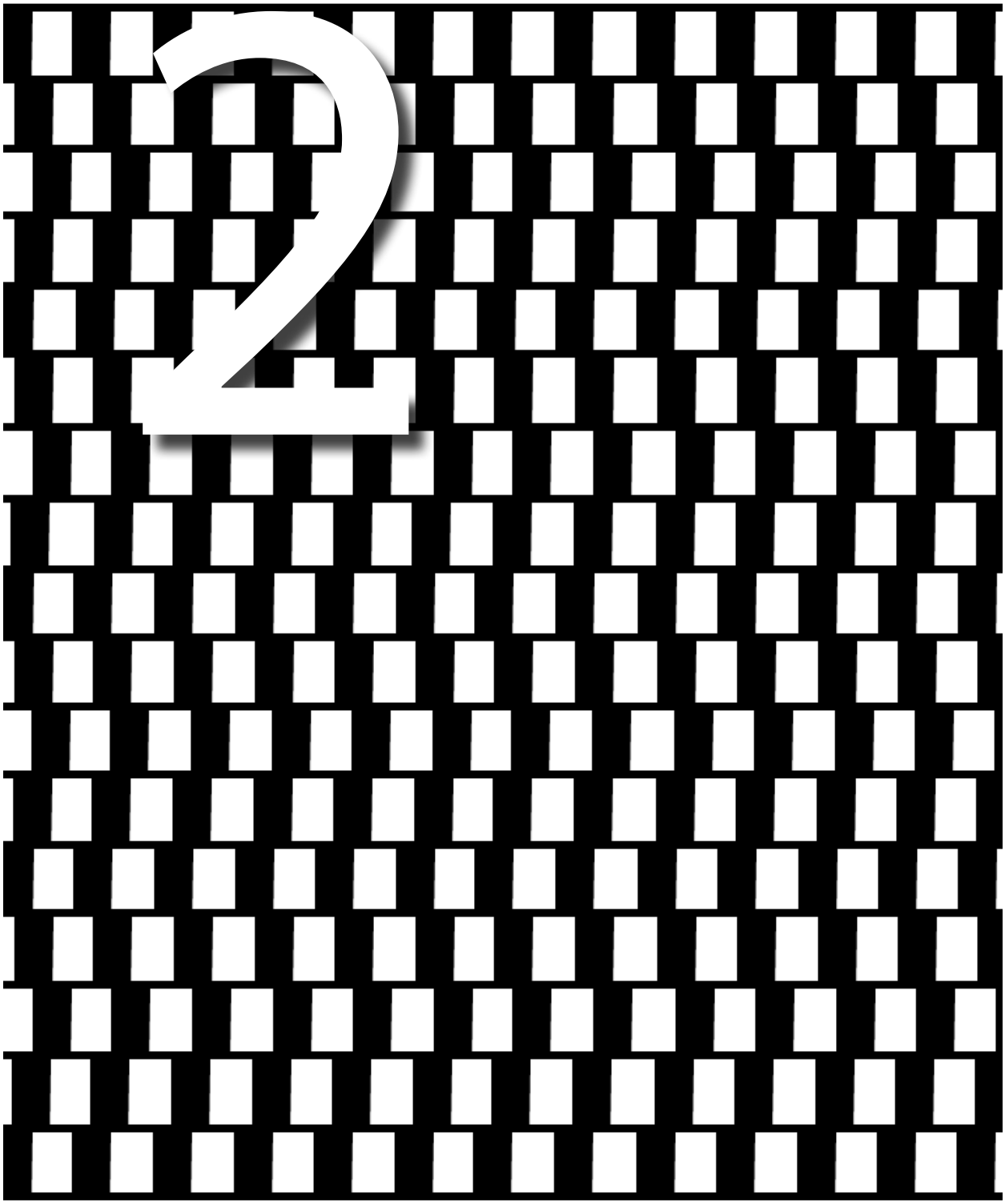

A literature review of ^{18}F-sodiumfluoride PET/CT and ^{18}F-fluorocholine or ^{11}C-choline PET/CT for detection of bone metastases in patients with prostate cancer

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ABSTRACT

Introduction

Although the detection of early bone metastases in men with prostate cancer remains a challenge in today's medicine, current guidelines state that bone scintigraphy with ^{99m}Tc-phosphonates (BS) is the most sensitive method for assessing bone metastases in these patients. In general, it is stated that bone scintigraphy has reasonable sensitivity and low specificity. The aim of this study was to present a review of the contemporary literature on the performance of ^{18}F-sodiumfluoride (NaF) and ^{11}C-choline or ^{18}F-fluorocholine and to reconsider the arguments based on which the present European and US guidelines are founded.

Methods

A literature search was conducted using the Medline database. Data were taken from eligible studies and the level of evidence was scored. Data were pooled to calculate the weighted sensitivity and specificity.

Results

Thirteen studies were eligible for inclusion in this review. On a lesion basis, we found a sensitivity and specificity of 84.0 and 97.7% for ^{11}C-choline and ^{18}F-fluorocholine and 88.6 and 90.7% for NaF, respectively. On a patient basis, the sensitivity and specificity were 85.2 and 96.5% for ^{11}C-choline and ^{18}F-fluorocholine and 86.9 and 79.9% for NaF, respectively. No significant differences were found between the sensitivity and specificity of ^{11}C-choline or ^{18}F-fluorocholine and NaF. There was large inconsistency in the reported sensitivity (range 39–100%) and specificity (range 57–80%) for BS.

Conclusion

The literature provides evidence for superior detection of bone metastases by both NaF PET and ^{18}F-fluorocholine or ^{11}C-choline PET with or without computed tomography (CT) compared with conventional BS. Guidelines should include NaF PET/CT and ^{11}C-choline or ^{18}F-fluorocholine PET/CT as alternatives for BS for the detection of bone metastases in patients with prostate cancer.

INTRODUCTION

Prostate cancer is the most common type of cancer in European men, with an incidence of almost 340 000 new cases and over 70 000 deaths every year (European Cancer Observatory, http://eu-cancer.iarc.fr/). There is considerable heterogeneity in the aggressiveness of the disease, and not all patients require immediate treatment. Metastases of more aggressive tumours are mainly found in skeletal tissue. Approximately 4% of all patients have metastasized disease at initial presentation, and, despite successful treatments for localized prostate cancer,~40% of men experience a detectable rise in prostate-specific antigen (PSA) within 10 years of treatment, signalling the persistence of (neoplastic) prostate tissue. Over time, bone metastases are detected in 65–75% of these patients (1–4), and in 85% of the patients who die of prostate cancer the axial skeleton is involved (5).

The early diagnosis of skeletal involvement in prostate cancer is crucial for appropriate patient management, in particular for the proper selection of therapy and follow-up care. This may prevent complications such as pathological fractures and spinal cord compressions that lead to considerable morbidity and a reduced quality of life (6). The presence of metastatic bone disease in patients with prostate cancer has a marked influence on the prognosis. The reported 5-year relative survival for patients with localized disease or with a regional spread to lymph nodes only is 100%. For patients with bone metastases, however, the survival decreases to about 28% (5). The median survival time for patients with bone metastases is 5 years. When castrate-resistant metastatic disease is present, the 1-year survival decreases to about 24%, with a median survival of only 8–18 months (7).

The diagnostic staging of patients with high-risk prostate cancer or with a biochemical relapse remains challenging in today's medicine. According to European and US guidelines, bone scintigraphy with ^{99m}Tc-phosphonates (BS) remains the most sensitive method for assessing bone metastases, being superior to clinical evaluation, bone radiographs, serum alkaline phosphatase measurement, and prostatic acid phosphatase determination (8–10). This is a grade B recommendation, according to the grades of recommendation defined by the Oxford Centre for Evidence-based Medicine (Table 1, http://www.cebm.net/). Wide ranges have been reported for sensitivity and specificity, from less than 50% to up to 100%. In general, it is stated that bone scintigraphy has reasonable sensitivity and low specificity. The reported poor accuracy of BS has incidentally led to a decrease in the use of this imaging modality in some countries, as well as in high-risk patients, who therefore proceed to treatment without having undergone an appropriate imaging evaluation (11). Improvement in diagnostic staging requires enhanced detection and more accurate characterization of bone metastases.

In recent years, Positron Emission Tomography (PET) has become a cornerstone in oncological imaging. The most widely used tracer, ^{18}F-fluorodeoxyglucose (FDG), has proved to be useful in a variety of cancers but is of limited value in prostate cancer

patients (12, 13). More recent PET tracers such as ^{18}F-sodiumfluoride (NaF) and ^{11}C-choline or ^{18}F-fluorocholine have shown promising results (12–26). The rationale for the better diagnostic performance of these tracers compared with BS lies in the possibility of using PET technology as well as in their biological kinetics. PET technology using ^{18}F-labeled or ^{11}C-labeled radiotracers results in enhanced imaging quality when compared with planar scintigraphy or single-photon emission computed tomography (SPECT), which use BS. Because of its biological kinetics, the bone tracer NaF has a three-fold better target-to-background ratio when compared with ^{99m}Tc-phosphonates (27–30). Both NaF and ^{99m}Tc-phosphonates are bone tracers that show elevated accumulation only at sites with elevated bone turnover. Thus, malignant depositions are exposed only because of a secondary bone reaction. Choline is a precursor for phospholipids that are needed for the formation of cell membranes (31). In contrast to NaF and ^{99m}Tc-phosphonates, the tracers ^{18}F-fluorocholine or ^{11}C-choline directly target tumour cells, and thus choline may detect bone metastases that have not yet affected the surrounding bone tissue.

Table 1. Oxford Centre for Evidence-based Medicine grades of recommendation.

A	Consistent level 1 studies
B	Consistent level 2 *or* 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 *or* 3 studies
D	Level 5 evidence or troublingly inconsistent *or* inconclusive studies of any level

"Extrapolations" are where data is used in a situation, which has potentially clinically important differences than the original study situation.

NaF and ^{11}C-choline or ^{18}F-fluorocholine have already been mentioned in the guidelines; however, these guidelines state that the quality of evidence in today's literature is insufficient to draw definitive conclusions, and therefore no final recommendations can be made (9–11). The aim of this study was to review the present relevant literature on the performance of NaF and ^{11}C-choline or ^{18}F-fluorocholine in the detection of bone metastases in prostate cancer and to reconsider the arguments based on which the present European and US guidelines are founded.

MATERIAL AND METHODS

Literature search and eligibility of studies

A comprehensive literature search was performed using the Medline database to identify relevant articles. We used various search algorithms based on a combination of the following terms: prostate, cancer, bone, metastasis, metastases, PET, Choline, and Fluoride. No language restrictions were applied. All articles reporting data on the diagnostic performance of NaF PET or PET/computed tomography (CT) or ^{11}C-choline or ^{18}F-fluorocholine PET or PET/CT for the detection of bone metastases in patients with prostate cancer were considered relevant.

The following studies were excluded from this review: studies that did not report data about the performance of NaF and/or ^{11}C-choline or ^{18}F-fluorocholine PET or PET/CT; studies presenting data about a patient population that was believed to have been used in earlier publications; studies reporting data about heterogeneous patient populations that varied in their primary cancer type without results for the prostate cancer group alone; studies for which no full-text article was available; studies conducted before January 2000; studies about the usefulness of NaF PET and/or ^{11}C-choline or ^{18}F-fluorocholine PET for therapy follow-up; review articles; letters to the editor; and case reports.

Data extraction

Data including author names, year of publication, study design, number of studied patients, characteristics of included patients, reported performance of the studied imaging modalities, data type (patient-based or lesion based), number of reviewers who interpreted the images, background of the reviewers (nuclear medicine physicians or radiologists), definition of a positive finding, used reference standard (RS), and definition of positive/negative final diagnosis were extracted from eligible studies. When articles did not report sensitivities, specificities, and positive and negative predictive values (PPV and NPV), they were calculated from the presented data when possible.

Level of evidence

Each article was critically appraised by two nuclear medicine physicians (M.W. and F.Z.), and the level of evidence was scored as per the criteria for diagnostic procedures as defined by the Oxford Centre for Evidence-based Medicine (http://www.cebm.net/) on the basis of whether: the studied patient populations were representative; good RSs had been used; the RSs had been applied to all patients and regardless of the index test result; index and reference tests had been compared blindly; the study could be reproduced on the basis of the described methods; and test characteristics were reported. On the basis of these criteria, the studies were classified as per the level of evidence categories ranging from 1 to 5, and a grade of recommendation was determined.

Statistical analysis

For evaluating the efficacy of NaF on a lesion basis, that of NaF on a patient basis, of ^{11}C-choline or ^{18}F-fluorocholine on a lesion basis, and of ^{11}C-choline or ^{18}F-fluorocholine on a patient basis, the collected data were pooled to calculate the weighted sensitivity and specificity using IBM SPSS statistics 20 (IBM Netherlands, Amsterdam, the Netherlands). Significant differences between categories were tested using an independent-sample t-test.

RESULTS

The search strategy used resulted in 2096 hits in the Medline database (Table 2). Screening of all titles and abstracts resulted in the selection of 69 potentially relevant articles. Screening of the reference lists of those articles yielded no extra relevant articles. After careful evaluation, 13 studies were found to be eligible for inclusion in this review. Eight articles provided data on the performance of NaF PET/CT compared with other imaging tools and a RS; three of these articles compared NaF PET/CT and ^{18}F-fluorocholine or ^{11}C-choline PET/CT, and the remaining five articles reported results of comparative studies between ^{18}F-fluorocholine or ^{11}C-choline PET/CT and other imaging tools and a RS.

Table 2. Literature search.

Search terms	Hits (N)
Prostate AND cancer AND PET	769
Prostate AND bone AND metastases AND PET	119
Prostate AND bone AND metastasis AND PET	60
Prostate AND bone AND fluoride AND PET	23
Fluoride AND metastases	174
Fluoride AND prostate AND cancer	85
Prostate AND bone AND choline AND PET	62
Choline AND metastases	316
Choline AND prostate AND cancer	488

Used search terms for literature search in the Medline database on www.pubmed.com.

After critical appraisal, a level of evidence was assigned to all articles. Ten articles reached a level of evidence of 3b, and three articles reached level 4, as defined by the Oxford Centre for Evidence-based Medicine (Table 3). None of the studies were assigned a higher level of evidence because of the general lack of a good RS, as application of the gold standard, which is histopathological confirmation of all lesions, is unethical and practically impossible. For three studies, a level of evidence of 4 was assigned, as no RS or an inconsistently applied RS was used and no test characteristics were reported.

There is considerable heterogeneity between the studies, including in terms of patient characteristics (Table 4) and study design. To provide a clean overview, the included studies are discussed separately in this section, and subsequently the results of the pooled data of the four categories are presented.

Table 3. Critical appraisal.

Author	Even-Sapir	Beheshti	Beheshti	Fuccio	McCarthy	Langsteger	Withofs	Picchio	Iagaru	Jadvar	Mosavi	Fuccio	Kjolhede
Year of publication	2006	2008	2009	2010	2011	2011	2011	2012	2012	2012	2012	2012	2012
Study setup	Pro	Pro	?	Retro	Pro	Pro	Pro	Retro	Pro	Pro	Pro	Retro	Pro
Representative patient population	Yes	Yes	Yes	Select	?	?	Yes	Select	?	Yes	Yes	Yes	Yes
Good reference standard	No	No	No	No	No	No	No	No	No	No	No	No	No
Reference standard applied to all patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Blind comparison index tests with reference	No	No	?	?	Yes	Yes	Yes	?	No	No	Yes	No	No
Reproducibility	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Test characteristics reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Level of evidence	**3b**	**3b**	**3b**	**3b**	**3b**	**3b**	**3b**	**3b**	**3b**	**3b**	**3b**	**4**	**4**

Critical appraisal according to guidelines of the Oxford centre for evidence based medicine levels of evidence. Pro = prospective, retro = retrospective, select = selection bias possible.

Table 4. Patients characteristics.

Author		Even-Sapir	Beheshti	Beheshti	Fuccio	McCarthy	Langsteger	Withofs	Picchio	Iagaru	Jadvar	Mosavi	Fuccio	Kjolhede
Year of publication		2006	2008	2009	2010	2011	2011	2011	2012	2012	2012	2012	2012	2012
Number of patients		44	38	70	25	26	40	10	78	18	37	49	123	90
Age		71.6* ± 8.8§	69* ± 8§	68* ± 7§	70.2* 58-80‡	75.4* 62-89‡	66* 51-82‡	n.s.	69* 47-82‡	n.s.	71.1# 53.8-86.9‡	67# 57-80 ‡	67.6* 54-83‡	66.8# 49.9-77.3‡
Newly diagnosed		25	17	32	0	0	17	0	0	0	0	49	0	90
Relapse		19	21	38	25	26	23	20	78	18	37	0	123	0
Previous therapy with curative intent	RP	n.s.	21	n.s.	20	n.s.	n.s.	n.s.	66	n.s.	26	0	123	0
	PP	n.s.	0	n.s.	4	n.s.	n.s.	n.s.	0	n.s.	0	0	0	0
	EBRT	n.s.	0	n.s.	1	n.s.	n.s.	n.s.	12	n.s.	11	0	0	0
Hormone therapy		n.s.	21	38	n.s.	26	n.s.	5	46	n.s.	4	0	22	0
PSA (ng/ml)	Newly diagnosed	>20	56* ± 64‡	39.7# 0.1-239‡	0	0	n.s.	0	0	n.s.	0	14# (1.3–950) ‡	0	22.0# (2.4-95)‡
	Relapse	n.s.			6.3# 0.2-37.7‡	10.5# 1.6-250‡	n.s.	> 20	21.1* 0.2-500‡	n.s.	3.2# (0.4-40.2)‡	0	3.3* 0.2-25.5‡	0

* Mean, #Median, ‡Range, §Standard deviation, n.s. = not specified, RP = radical prostatectomy, PP = partial prostatectomy, RT = radiation therapy.

NaF PET

Even-Sapir et al. (14) prospectively studied the performances of conventional planar bone scintigraphy with ^{99m}Tc-MDP, combined planar scintigraphy and SPECT with ^{99m}Tc-MDP, NaF PET, and NaF PET/CT in high-risk prostate cancer patients (Gleason ≥8, PSA ≥20 ng/ml or nonspecific sclerotic lesions on CT). Their article presents the performances of the studied techniques on a patient and lesion basis. For both of these categories two types of analyses were used. In the first analysis it was assumed that equivocal lesions on the index test were positive for metastases. In contrast, the second analysis assumed that equivocal lesions were negative for metastases. The performances of each technique are listed in Table 5. In both patient-based and lesion-based analyses, addition of SPECT to planar imaging increased the overall performance of the technique. In addition, a random subgroup of 24 patients underwent a multi-field of view (FOV) axial-body SPECT instead of a single-FOV SPECT, which resulted in an even better diagnostic performance. In this subgroup, NaF PET was found to be more sensitive (100 vs. 92%), with a higher NPV (100 vs. 90%), compared with ^{99m}Tc-MDP multi-FOV SPECT; no difference in specificity (82 vs. 82%) and PPV (87 vs. 86%) was found. The best performance was found for NaF PET/CT, with a sensitivity, specificity, PPV, and NPV of 100%. However, it must be noted that this high performance may be because CT was part of both the index test and the RS.

Withofs et al. (15) prospectively compared conventional ^{99m}Tc-MDP whole-body scintigraphy combined with single-FOV SPECT (thoracic or lumbar region) against NaF PET/CT in 34 patients, of whom 10 patients had prostate cancer with suspicion of bone metastases (PSA>20 ng/ml, N=9; clinical suspicion, N=1) and 24 patients had breast cancer. The performances of the studied imaging tools are presented separately for the 10 patients with prostate cancer on both patient and lesion bases, and equivocal lesions are considered either positive or negative, similar to the above-mentioned study. The reported sensitivity of NaF PET/CT was superior to that of conventional bone scintigraphy (Table 5) and its accuracy was significantly superior.

In a group of 52 patients, among whom 18 had prostate cancer, Iagaru et al. (20) prospectively evaluated the detection of skeletal metastases with planar ^{99m}Tc-MDP scintigraphy, NaF PET/CT, and ^{18}F-FDG PET/ CT. For patients with prostate cancer, this trial demonstrates the superiority of NaF PET/CT over ^{18}F-FDG PET/CT and ^{99m}Tc-MDP scintigraphy in the detection of bone metastases (Table 5). In one patient, ^{18}F-FDG PET/CT showed extra osseous lesions, whereas the extensive skeletal metastases, positive on NaF PET/CT, were missed.

Table 5. Diagnostic characteristics of the index tests.

	Even-Sapir			**Beheshti**	**Beheshti**	**Fuccio**	**McCarthy**	**Langsteger**		**Withofs**	**Picchio**	**Iagaru**	**Jadvar**	**Mosavi**
Year of publication	2006			2008	2009	2010	2011	2011		2011	2012	2012	2012	2012
Analysis (patient or lesion basis)	Patient	Lesion	Subgroup*	Lesion	Lesion	Patient	Lesion	Patient	Site‡	Lesion	Patient	Unclear	Patient	Patient
Number (patients or lesions)	44	156	24	321	318	25	26	40	360	386	78		37	49
Studied Modalities														
Planar BS														
Sensitivity	70	39	69								100	88		
Specificity	57	83	64								75	80		
PPV	64	56	69								68			
NPV	55	70	64								100			
Accuracy											83			
Planar BS + single FOV SPECT														
Sensitivity		61								67				
Specificity		87								82				
PPV		73								53				
NPV		80								89				
Planar BS + SPECT axial skeleton														
Sensitivity		71#	92											
Specificity		85#	82											
PPV		73#	86											
NPV		83#	90											
^{18}F- or ^{11}C-Choline PET/CT														
Sensitivity				74	79	86	96	91	90		89			

Specificity				99	97	100	100	89	96		98			
PPV						100	100				96			
NPV						50	74				94			
Accuracy				85	84			90	95		95			
NaF PET														
Sensitivity	100	100	100											
Specificity	62	79	82											
PPV	74	73	87											
NPV	100	100	100											
NaF PET/CT														
Sensitivity	100	100	100	81				81	87	100		100	43	100
Specificity	100	100	100	93				93	94	90		80	83	91
PPV	100	100	100							75			60	56
NPV	100	100	100							100			70	100
Accuracy				86				88						
^{18}F-FDG PET/CT														
Sensitivity												56	21	
Specificity												100	100	
PPV													100	
NPV													68	
DW-MRI														
Sensitivity														100
Specificity														98
PPV														83
NPV														100

If an article reports performances for both equivocal lesions considered malignant and equivocal lesions considered benign, the performance for equivocal lesions considered malignant are reported. # Group of 112 lesions, * Subgroup of 24 randomly patients in which a SPECT was performed for the whole axial skeleton, ‡ Nine sites of the skeleton were analysed: cervical spine, Th1-Th6, Th7-Th12, lumbar spine, ribs + sternum, pelvis, upper extremities, lower extremities and other bones. NaF = ^{18}F-sodiumfluoride.

Jadvar et al. (21) prospectively evaluated the detection of occult metastases by NaF PET/CT and ^{18}F-FDG PET/CT in 37 patients with a biochemical recurrence of prostate cancer (PSA 0.5–40.2 ng/ml). All patients had negative or indeterminate planar bone scintigrams and negative CT scans of the chest, abdomen, and pelvis. From the given data, the sensitivity, specificity, PPV, and NPV for bone metastases were calculated on a patient basis (Table 5). For one patient, only ^{18}F-FDG PET/CT was positive for retroperitoneal lymph nodes. In eight patients, only NaF PET/CT was positive, showing randomly distributed skeletal lesions. However, according to the RS, four of these findings were false positives. Both scans were positive but inconsistent in two patients, both of whom had skeletal lesions on NaF PET/CT that were missed on ^{18}F-FDG PET/CT. In one of these patients, only one of five osseous lesions identified on NaF PET/CT was also positive on ^{18}F-FDG PET/CT. In the other patient, NaF PET/CT was positive for one osseous lesion, whereas ^{18}F-FDG PET/CT was positive for lymph nodes. However, it must be noted that for 23 of 37 patients no follow-up imaging was attainable, and for these patients the RS was based on whether the clinician felt compelled to alter the clinical management on the basis of the results of the ^{18}F-FDG and NaF PET/CT scans.

Mosavi et al. (32) prospectively studied the performance of NaF PET/CT and whole-body diffusion weighted MRI (DW-MRI) in 49 patients with newly diagnosed prostate cancer who also had a Gleason score of at least 8. Five patients had skeletal metastases according to the RS. Both NaF and DW-MRI scans showed metastases in all five patients. False-positive findings were reported in four patients on NaF PET/CT and in one patient on DW-MRI. On a patient basis, there were no false-negative findings (Table 5). A lesion-based analysis showed a higher number of metastases on NaF PET/CT compared with DW-MRI in four of five patients. The authors concluded that, although DW-MRI has higher specificity compared with NaF, it is less sensitive.

^{18}F-fluorocholine or ^{11}C-choline PET

Beheshti et al. (12) evaluated the performance of ^{18}F-fluorocholine PET/CT in 70 patients in correlation with changes on CT. In their study, 32 patients had newly diagnosed prostate cancer and a Gleason score of at least 7 or elevated PSA (>10 ng/ml) and 38 patients had suspicion of metastases after a previous radical treatment. Some of their patients had already received hormonal therapy, chemotherapy, or radiation therapy. A sensitivity of 79%, specificity of 97%, and accuracy of 84% were reported for ^{18}F-fluorocholine PET/CT (Table 5). Overall, 262 lesions showed increased ^{18}F-fluorocholine uptake, of which 210 were interpreted as malignant on the basis of the pattern of ^{18}F-fluorocholine uptake and CT findings (207 true positives and three false positives). Of the 207 proven malignant lesions that were positive on ^{18}F-fluorocholine PET, 49 (24%) showed no morphological changes on CT. A striking finding is the negative correlation between progressive sclerosis, as seen after the initiation of hormone therapy, and ^{18}F-fluorocholine uptake in malignant lesions with Hounsfield units of less than 825 ($r = -0.52$, $P<0.001$). None of the sclerotic lesions with Hounsfield units greater than 825 showed ^{18}F-fluorocholine uptake.

Fuccio et al. (18) retrospectively reported on the performance of ^{11}C-choline PET/CT in 25 patients with a biochemical relapse of prostate cancer. In their study, all patients were found to have one equivocal lesion on planar and/or SPECT with ^{99m}Tc-DPD. A total of 22 patients were classified as being positive for the presence of metastatic bone lesions, and in 19 patients these lesions were found on ^{11}C-choline PET/CT (Table 5). Multiple sites of metastases were found on ^{11}C-choline scans in 11 patients: multiple bone lesions in six patients, a single bone lesion and extra osseous localizations (local recurrence in one patient and lymph node lesions in the other) in two, and multiple bone lesions and extra osseous malignancies (lymph nodes in one patient, lung metastasis in one patient, and an unexpected bronchi alveolar carcinoma in the third patient) in three patients. Of the 50 true-positive lesions, 24 were evident on CT images. Three ^{11}C-choline PET-negative lesions were classified as positive on the basis of characteristic abnormalities on CT images.

The performance of ^{18}F-fluorocholine PET or PET/CT in metastasis detection was analysed in a study comprising 26 castration-resistant patients (androgen therapy with castrate levels of testosterone) by McCarthy et al. (24). In their study, an ^{18}F-fluorocholine PET was performed for 13 patients, whereas PET/CT was used for the other 13. A sensitivity, specificity, PPV, and NPV of, respectively, 96, 100, 100, and 74% were found. Of all 142 proven malignant lesions in the bone, the ^{18}F-fluorocholine PET gave positive results for 136 lesions, of which none were false positive.

Fuccio et al. (19) studied the added value of ^{11}C-choline PET/CT in 123 patients with a biochemical relapse after radical prostatectomy and with no signs of bone metastases on conventional BS. Findings on ^{11}C-choline PET/CT were considered positive if they were confirmed by a positive biopsy or on BS, CT, or MRI within 6 months after the ^{11}C-choline PET/CT scan. Positive findings were also considered to be true positive in the occurrence of normalization on ^{11}C-choline PET/CT following systemic therapy or when progression of disease was detected in follow-up imaging studies. In their study, a total of 30 previously unknown lesions were detected in 18 of 123 patients (14.6%). The majority of these lesions were located in the ischium or pubic bone (13/30), nine of 30 were located in the sacrum or lumbar spine, and three of 30 were located in the ribs. Ten of these lesions showed no structural or morphological abnormalities on CT images. A total of 24 patients without bone lesions had extra osseous malignant lesions (20 lymph node metastases, one lung metastasis, and three local relapses). It has to be mentioned that the interval between BS and ^{11}C-choline PET/CT (mean, 2.5 months; maximum, 4 months in some cases) might explain some of the differences found between the two modalities in the detection of osseous lesions.

Seventy-eight patients with a biochemical relapse after radical therapy were retrospectively evaluated by Picchio et al. (25). Patients who underwent both BS and ^{11}C-choline PET/CT within a period of 3 months were eligible for analysis. For equivocal lesions considered positive, a patient-based analysis revealed scores of 89, 98, 96, and

94% for sensitivity, specificity, NPV, and PPV, respectively (Table 5). Positive ^{11}C-choline lesions were detected in 24 of 78 patients. All of these findings were confirmed as true positive according to the RS. Three false negative cases were reported. In one patient, the ^{11}C-choline scan was negative, whereas the BS scan showed a positive lesion. In the other two patients, lesions at the rib level were undetected, whereas they were documented using CT or radiography, which were performed specifically because of inconclusive BS findings. Equivocal findings were reported for one patient (1%) on ^{11}C-choline PET/CT and for 21 patients (27%) on BS scans. For these 21 patients, the ^{11}C-choline PET/CT provided true-negative results in 13, false negative results in two, and true-positive results in six patients.

NaF PET and ^{18}F-fluorocholine or ^{11}C-choline PET

Beheshti et al. (17) presented a prospective study using ^{18}F-fluorocholine PET/CT and NaF PET/CT in 17 high-risk patients with newly diagnosed prostate cancer and 21 patients with evidence of progression or clinical suspicion of bone metastases. The results of both NaF PET/ CT and ^{18}F-fluorocholine PET/CT, on a lesion basis, are reported in Table 5. Although NaF scans identified more lesions in some patients compared with ^{18}F-fluorocholine scans, no alterations ensued in their clinical management. With respect to sensitivity, no statistically significant difference was found (p=0.12); however, ^{18}F-fluorocholine PET/CT showed significantly (p=0.01) higher specificity compared with NaF PET/CT. Of all malignant lesions, 53% were detected on both PET scans, 23% were detected on NaF PET scans only, 13% on ^{18}F-fluorocholine scans only, and 11% were undetectable on both PET scans. For patients on hormone therapy, 12% of the lesions were undetectable on both PET tracers, whereas for the patients not on hormone therapy only 6% were undetected with both PET tracers.

Langsteger et al. (23) prospectively compared the performances of NaF PET/CT and ^{18}F-fluorocholine PET/CT in a mixed group of 17 patients with newly diagnosed prostate cancer and 23 patients with suspected recurrence, all of whom had complaints of osteoarticular pain. A patient-based and a site-based analysis showed good diagnostic performance for both radiopharmaceuticals (Table 5). Although the patient-based analysis showed no significant differences, the lesion-based analysis showed a significantly better specificity for ^{18}F-fluorocholine PET/CT (p=0.034).

In a prospective setting, Kjolhede et al. (22) studied the added value of ^{18}F-fluorocholine PET/CT and NaF PET/CT in staging high-risk prostate cancers (PSA 20–99 ng/ml and/or Gleason 8–10 tumours) in 90 patients with normal or equivocal findings on ^{99m}Tc-MDP planar scintigraphy and CT, who were scheduled for therapy with curative intent. In 50 of the 90 included patients, one or both PET/CT scans indicated bone and/or lymph node metastases. Bone metastases were suggested in 37 patients on NaF PET/CT, 19 of whom showed evidence for multiple bone lesions. The NaF scan revealed possible bone metastases in 15 patients with a negative ^{18}F-fluorocholine PET/CT. All skeletal lesions found on ^{18}F-fluorocholine scans were also positive on NaF scans. Therefore, from this

study it was concluded that PET/CT with ^{18}F-fluorocholine and/or NaF is capable of detecting metastases in patients with high-risk prostate cancer and with a negative or inconclusive bone scan. The ^{18}F-fluorocholine scan indicated lymph node metastases in 13 patients with undetected skeletal lesions on both NaF PET/CT and ^{18}F-fluorocholine PET/CT. For 20% of the studied patients, the metastatic spread was considered too extensive for curation, and hence the treatment plan was changed to non-curative.

Pooled data

For this analysis, studies with a level 4 of evidence as well as the NaF PET/CT results reported by Even-Sapir et al. (14) have been excluded; however, the results of the NaF PET scans of their study have been included. On a lesion basis, we found a pooled weighted sensitivity and specificity of 84.0 and 97.7% for ^{11}C-choline and ^{18}F-fluorocholine PET/CT scans and 88.6 and 90.7% for NaF PET/CT scans, respectively (Table 6). On a patient basis, these calculated performances were, respectively, 85.2 and 96.5% for ^{11}C-choline and ^{18}F-fluorocholine and 86.9 and 79.9% for NaF. On both patient and lesion bases, we found no significant differences between the specificity of ^{11}C-choline and ^{18}F-fluorocholine PET/CT scans and NaF PET/CT scans for the pooled data (p=0.055 and 0.075, respectively), in contrast to the findings of Behesthi and Langsteger (17,23).

Table 6. Pooled data

Tracer	**Analysis**	**Sensitivity** (95%-CI interval)	**Specificity** (95%-CI interval)
^{11}C-choline or ^{18}F-fluorocholine	lesion basis	84.0 (83.5 – 84.5)	97.7 (97.6 – 97.8)
^{11}C-choline or ^{18}F-fluorocholine	patient basis	85.2 (83.8 – 86.6)	96.5 (95.8 – 97.1)
NaF	lesion basis	88.6 (88.1 – 89.1)	90.7 (90.4 – 91.1)
NaF	patient basis	86.9 (83.7 – 90.0)	79.9 (78.4 – 81.4)

Sensitivities and specificities on patient and lesion basis for ^{11}C- or ^{18}F-fluorocholine PET/CT and ^{18}F-sodiumfluoride (NaF) PET/CT for detection of bone metastases in prostate cancer.

DISCUSSION

Reports in today's literature about the diagnostic performances of different imaging modalities for the detection of bone metastases in prostate cancer are heterogeneous in many aspects and include relatively small cohorts. Differences seen in the included patient population relate to: the stage of the disease, administration of previous therapy, PSA levels, Gleason scores, and implementation of certain imaging modalities before inclusion in the study. Considerable heterogeneity is also found in the RS used. As a result of ethical reservations, the gold standard, which is histopathological examination of all abnormal lesions, has not been used in any of these studies and is not expected to be used in any future studies. Therefore, different authors considered different RSs to

be the most suitable for their study, although all of them come with certain advantages and disadvantages. Noteworthy is the use of CT as part of the RS by Even-Sapir et al. (14), as CT is also part of one of the index tests, and this probably resulted in the sensitivity, specificity, PPV, and NPV of 100% for NaF PET/CT scans. Beheshti et al. (12, 17) excluded the positive lesions on NaF PET/CT and ^{18}F-fluorocholine PET/CT for which no final diagnosis could be made on the basis of the RS. Thereby, the most interesting lesions, for which possibly only NaF PET/CT or ^{18}F-fluorocholine PET/CT could provide a diagnosis, were excluded from the analysis. In other studies, the use of the RS may be accountable for a number of reported false-positive findings, as the used index test may be better than the used RS. Therefore, the actual specificity of NaF PET/CT and ^{18}F-fluorocholine or ^{11}C-choline PET/CT scans may be higher than that reported.

In some studies, lesions clearly identified as bone metastases by CT but negative on ^{18}F-fluorocholine PET or NaF PET were considered 'false negative'. This qualification is arguable, as, in general, these lesions are found in patients treated with systemic therapy. Patients who respond to systemic therapy may show a progressive sclerotic appearance on CT but a decrease in choline or fluoride tracer uptake as a result of a diminished number or absence of tumour cells. Therefore, it could be stated that the CT is 'false positive' in these cases. As the accepted gold standard will not be used as a reference for every lesion found on imaging modalities, the quest for a suitable RS is probably more difficult than that for a better diagnostic imaging modality for bone metastases in prostate cancer. We suggest that a combination of histopathological examination and a follow-up period of 6–12 months, especially including the results of follow-up imaging (including MRI, CT, BS, and PET scans), is most suitable.

Despite these differences found in the studies and the inability to use the gold standard as a reference for all lesions detected on the tested imaging modalities, we found six articles for both NaF PET/CT and ^{11}C-choline or ^{18}F-fluorocholine PET/CT with a 3b level of evidence and without much inconsistency. Therefore, for both NaF PET/CT and ^{11}C-choline or ^{18}F-fluorocholine PET/CT, a grade B level of recommendation, the same as that for BS, could be given in the guidelines (http://www.cebm.net/).

Of interest, in the search for the best imaging modality for bone metastases, we found that most studies that compared NaF PET/CT and/or ^{18}F-fluorocholine or ^{11}C-choline PET/CT with BS used suboptimal acquisition protocols for bone scintigraphy. For example, none of the reviewed studies used SPECT/CT to study the axial skeleton. Probably the best acquisition protocol for BS in the included studies, a multi-FOV SPECT of the axial skeleton, was used by Even-Sapir et al. (14). In this study, a non-significant better performance of NaF PET without CT was detected (sensitivity 100% and specificity 82%) compared with ^{99m}Tc-MDP BS with SPECT of the axial skeleton (sensitivity 92% and specificity 82%). The added value of the combination of SPECT and CT was shown in a prospective diagnostic accuracy study by Zhao et al. (33); this study reported sensitivities of 82.5, 93.7, and 98.4% and specificities of 66.7, 80.8, and 95.7% for SPECT,

SPECT+CT, and SPECT/CT fusion, respectively. The performance of SPECT/CT in this study with a mixed oncological population corresponded with the performances of NaF PET/CT and ^{18}F-fluorocholine or ^{11}C-choline PET/CT in this review.

The literature regularly mentions the low availability of SPECT/CT cameras as an argument in favour of the use of suboptimal acquisition protocols for BS in the study presented. In contrast to this, we believe that SPECT/CT and PET/CT facilities will be widespread in western countries in the near future, if not already. According to this point of view and the reported high sensitivities and specificities of SPECT/CT for detecting bone metastases, the use of state-of-the-art ^{99m}Tc-phosphate- based SPECT/CT should be included in the discussion on which modality is the most suitable in standard clinical practice for this purpose in the near future.

An important aspect influencing the performance of an imaging modality is the method of interpretation of the images. Multiple studies used predefined diagnostic criteria. Thus, specific aspects of the lesions concerning the location of the lesions and congruent findings on CT have been taken into account. In general, studies that do not use predefined criteria report more equivocal lesions. More equivocal lesions were also found on conventional BS scans compared with NaF PET/CT or ^{18}F-fluorocholine or ^{11}C-choline PET/CT scans, and less inter-observer variability was reported for PET/CT modalities. In addition, it should be mentioned that the use of SPECT/CT instead of planar BS would probably result in more consistent results for BS. With respect to equivocal lesions, performance is assessed on the basis of two assumptions: these lesions are either considered positive for metastases or they are considered negative. Most studies report the performance for both assumptions. In this article, we have reported the performances only for equivocal lesions considered positive, as we assume that this strategy most resembles clinical practice.

Today's guidelines provide characteristics based on which patients should be classified as having a high risk for metastases. An important factor on which this classification is based is a PSA level of at least 20 ng/ml. This limit is particularly based on the finding that bone metastases are detected relatively more often in patients with a PSA of more than 20 ng/ml. A meta-analysis of 23 articles including 8644 patients by Abuzallouf et al. (34) revealed that bone metastases are detected in 2.3, 5.3, and 16.2% of patients with a PSA level of less than 10, 10.1–19.9, and at least 20, respectively. It should be noted that almost all included articles date from the pre-SPECT/CT era. Loeb et al. (35) published retrospectively acquired data that provided another perspective. In 193 patients who underwent a bone scan at least annually after radical prostatectomy for prostate cancer, they found that 26% of the patients had a PSA level of less than 10 ng/ml at the time of diagnosis of bone metastases. In light of the above-mentioned perspective and the suggestion that newer techniques, such as ^{99m}Tc-phosphonates SPECT/CT, NaF PET/CT, ^{18}F-fluorocholine PET/CT and ^{11}C-choline PET/CT, have better diagnostic performances, scanning of patients with PSA levels less than 20 ng/ml may become standard practice

in clinical management. The indication for screening of bone metastases may then be based more on absolute risk than on the chance of finding them. It must be mentioned that some guidelines also include the rate of doubling of the PSA value to estimate the risk for bone metastases, and thus a BS may be indicated for asymptomatic patients with a PSA level less than 20 ng/ml.

Besides the diagnostic performance, other aspects of the different imaging modalities should be taken into account to draw definite conclusions about the applicability of these modalities in standard clinical management. The commonly used arguments in favour of BS include relatively low cost, easy availability, and practical considerations, including a relatively short acquisition time for a whole-body image.

With respect to cost, the literature mentions high costs of PET imaging for bone metastases compared with routine BS as a major disadvantage. However, we believe that the referred costs are outdated, as a number of aspects have led to a decrease in the cost of PET/CT scans. First, the use of newer PET cameras and attenuation-correcting software has led to a decrease in the required doses of expensive PET tracers, thereby sometimes halving the cost of tracers. Moreover, the cost of radiopharmaceuticals per MBq is likely to decrease. These costs are highly dependent on the facilities within a nuclear medicine department or in the local area. Growing indications for PET tracers have made priming cyclotron facilities more cost-effective, and the start-up of more cyclotron facilities is ongoing in western countries. Further technical developments and higher demands have also led to the development of less expensive cyclotron facilities. On the basis of the above-mentioned arguments, it is likely that the cost of PET tracers, and hence of PET/CT scans, will decrease even more in the near future.

Since the recent shortage of ^{99}Mo/^{99m}Tc generators, the Nuclear Medicine Society has become aware of the consequences of such a shortage. Aging of existing reactors and delay in starting up new reactors imply that shortages are likely to occur in the future, which may result in an increase in the cost of ^{99}Mo/^{99m}Tc generators. The higher availability of cyclotron facilities and PET tracers makes nuclear medicine less dependent on products produced in reactors. With respect to the arguments and developments as described in the former two paragraphs, the use of PET/CT imaging for bone metastases may also become economically worthwhile.

With regard to the practical argument of the relatively fast acquisition of whole-body BS, it can be mentioned that several technical advancements have led to faster acquisition protocols for PET. These advancements comprise the following: the use of CT images for attenuation correction, which renders time-consuming transmission scans unnecessary; larger FOV of PET scanners; 3D PET acquisition; the introduction of time-of-flight PET scanners; and the introduction of more sensitive detecting crystals in PET cameras. The current acquisition time for whole-body PET/CT imaging is comparable to that of planar whole-body BS and is less time-consuming than whole-body SPECT/CT.

Although several of the above-mentioned aspects may be in favour of NaF PET/CT or ^{18}F-fluorocholine or ^{11}C-choline PET/CT, it will be difficult to clinically translate choline tracers in the large US market.

In addition, it should be mentioned that technical progress is being made for other imaging modalities, including morphological imaging with CT or whole-body MRI and PET modalities with tracers targeted on different pathways that may be upregulated in prostate cancer. Recently, promising diagnostic performances, sometimes better than those reported for NaF PET and ^{18}F-fluorocholine or ^{11}C-choline, have been shown for tracers of lipogenesis (^{18}F-acetate or ^{11}C-acetate), cellular proliferation (^{18}F-30-deoxy-30-fluorothymidine and ^{18}F-20-fluoro-5-methyl-1-b-D-arabinofuranosyluracil), gastrin releasing peptide receptor expression (^{68}Ga-bombesin analogues), amino acid metabolism, prostate-specific membrane antigen, and gene-mediated imaging (36). Although a lot of research is needed before these modalities can be applied in clinical management, these may be of value to standard prostate cancer imaging in the future.

CONCLUSION

The literature provides evidence for better detection of bone metastases using both NaF PET and ^{18}F-fluorocholine or ^{11}C-choline PET with or without CT compared with conventional BS scans. The sensitivities of both PET tracers were found to be comparable, although there are indications that the specificity of ^{11}C-choline or ^{18}F-fluorocholine is higher than that of NaF. It can be concluded that there is evidence (grade B of recommendation) that NaF PET/CT or ^{11}C-choline or ^{18}F-fluorocholine PET/CT scans can be used instead of BS scans. The eventual choice between BS or NaF PET/CT and ^{11}C-choline or ^{18}F-fluorocholine depends mainly on the equipment of the nuclear department and the availability of the tracers.

RECOMMENDATION

Guidelines should include NaF PET/CT and ^{11}C-choline or ^{18}F-fluorocholine PET/CT as alternatives for BS for the detection of bone metastases in patients with prostate cancer. Further trials are required to clarify whether today's indications for screening of bone metastases in these patients could be extended on the basis of a higher detection rate of NaF or ^{11}C-choline or ^{18}F-fluorocholinePET/CT scans for metastases in patients with PSA less than 20 ng/ml.

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